Medical and Pediatric Oncology Supplement 1:41–44 (1996)

Methodologic Issues in the Study of Second Malignant Neoplasms and Pregnancy Outcomes

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INTRODUCTION

The striking advances in the treatment of childhood cancer have been well-described [1]. Long-term survival will be achieved in more than two-thirds of children diagnosed with cancer in the United States [2]. Overall, approximately 70% of children with cancer before the age of 20 are surviving 5 years from diagnosis, although the relative 5-year survival rates vary according to diagnosis and race. For example, 5-year survival ranges from 89% for Wilms' tumor patients to 31% for patients with acute myeloid leukemia.

Since the marked improvement in the survival of childhood cancer patients generally began during the early 1970s, we are now in a position where the study of specific longterm outcomes becomes feasible on a large scale. Two of the areas of intense interest include the occurrence of late occurring secondary malignancies and pregnancy-related outcomes. While second neoplasms have been the focus of numerous studies, they have in general been confined to (a) cancer occurrence in the first decade following therapy and/or (b) confined to study populations of a relatively small size. With regard to pregnancy-related outcomes, there are a limited number of studies, a consequence of the recent nature of improved survivorship and thus the limited number of childhood cancer survivors in the childbearing age group. With the aging of the childhood cancer survivor population, studies of pregnancy outcomes are now becoming more feasible.

As investigators direct their attention to the study of late-occurring second malignancies and the reproductive outcomes in childhood cancer survivors, it is important to consider the methodologic issues that impact on the quality of the information generated. Briefly discussed below are selected issues relating to study design, assessment of risk, and analytic techniques. These issues are discussed within the context of the study of second malignancies and pregnancy outcomes. More detailed descriptions of the methodologic issues discussed are available in numerous texts and articles [3–7].

STUDY DESIGNS

Investigating the occurrence of and risk factors for a given outcome in a population can typically be accomplished through a variety of different study designs (Table I). The specific study design is highly dependent on both the nature of the outcome under investigation and the current state of understanding for the area of interest. If relatively little is known about the etiology of a disease, a descriptive study can often provide information important for hypothesis generation.

Generally, hypothesis testing is accomplished by the conduct of analytic studies, although hypothesis generation can also be the objective of analytic study designs. It is possible to utilize either an observational or experimental approach to study design in analytic studies. Experimental studies (i.e., clinical trials) have the advantage of incorporation of a randomized design to investigate the impact of specific exposure(s) or treatments. Experimental designs are not generally used in the study of late effects. Exceptions include Phase III clinical trials of cancer therapy that are designed to address a late-effects question (i.e., impact of reduction of therapy) or secondary intervention studies (i.e., use of cardio-protectants to modify anthracycline-induced myocardial dysfunction).

The most commonly conducted analytic studies include the case-control and cohort designs. A case-control study involves the identification of two groups of study subjects: (a) cases, defined as individuals (i.e., survivors) with the outcome of interest (e.g., second malignancy); and (b) controls, defined as individuals in whom the outcome of interest has not occurred and are identified from the same general population from which the cases arose. Data collection on individuals from the two groups

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TABLE I. Study Designs to Investigate Late Effects in Childhood Cancer Survivors

Descriptive	Appropriate when little is known regarding the occurrence of a specific outcome.
Cross-sectional	Lacks longitudinal data, with outcome and exposure generally ascertained at the same time.
Case-control	Typically efficient approach but is subject to bias. Restricts scope of a study to one outcome.
Cohort	Allows direct study of multiple outcomes, calculation of incidence and relative risk but is generally more costly to conduct.
Nested case-control	Requires availability of a well-defined cohort but can represent a highly efficient manner to study risk factors that may be difficult to ascertain for an entire cohort.
Case-cohort	Requires availability of a well-defined cohort. Best for collection of data that would be difficult or too costly to obtain for the entire cohort.
Clinical trials	Infrequently used for studies of late effects but appropriate for therapeutic studies with a late effects question of testing of secondary intervention strategies.

are then compared. Case-control studies have a number of advantages including the fact that they are often less expensive and quicker to complete. On the other hand, the case-control study can represent a serious challenge since the method is prone to bias, usually resulting from selection of the control group or collection of data from cases and controls.

A cohort study involves classification of study subjects into groups based on a given characteristic (or group of characteristics) with subsequent observation over time to determine the occurrence of a specific outcome(s). Within the context of late effects, the individuals are usually classified into groups based on the type cancer and/or the type of therapy they received. It is important to recognize that a cohort of patients can be assembled either prospectively or retrospectively. A retrospective cohort design has an advantage. Typically one does not have to wait for an extended length of time to achieve adequate follow-up of the cohort in order to allow a sufficient number of events to occur. When a well-defined cohort of patients has been established, there are times where it is desirable to conduct a case-control study within the cohort (also referred to as a nested case-control study). The design of a nested case-control study often has the advantage of being more efficient when it is not possible to collect specific information on all members of the cohort.

Another analytic study design, which is much less frequently used, is that of a case-cohort design. In this situation, a cohort of patients is used to investigate risk factors for a specific outcome or series of outcomes. From within the cohort, a subsample (i.e., sub-cohort) is identified and detailed information is obtained. Individuals within the entire cohort who experience the outcome of interest (i.e., cases) are then compared to the sub-cohort. As with the nested case-control study the case-cohort design can increase the efficiency of a study when it is difficult or costly to obtain the information of interest on all members of the cohort.

The cross-sectional study design utilizes the identification of a population for whom exposure and disease status are simultaneously determined. This approach is frequently used in the study of late-effects and is likely the result of (a) the lack of access to a well-defined cohort, (b) the conduct of studies within populations being seen in a specific setting, such as late-effects clinics, and (c) the interest in addressing a specific question within a relatively short period of time.

ASSESSMENT OF RISK

Within epidemiologic research, the primary measure of association between an outcome and a putative risk factor is through the use of the relative risk. A relative risk is defined as the ratio of incidence rate of the outcome for those with the risk factor (e.g., a specific exposure or characteristic) to the incidence rate for persons without the factor of interest. The relative risk can be calculated from a cohort study since the incidence is known for the groups of interest. However, within a case-control study it is not possible to determine the incidence of the outcome and thus it is necessary to estimate the relative risk by use of the odds ratio (also referred to as the relative odds or cross-product ratio but frequently referred to as, simply, the relative risk). Since the relative risk is a ratio, a value of 1.00 indicates no increased or decreased risk. For example, a relative risk of 3.5 is interpreted as indicating that individuals with the exposure display a 3.5-fold increased risk of experiencing the outcome.

Another measure of risk often used in studies of late effects is the standardized rate ratio including the standardized mortality ratio (SMR) or the standardized incidence ratio (SIR). Both of these measures represent a method of rate adjustment. A SMR or SIR is derived by

comparing the observed number of events with an expected number calculated by applying rates from a large, known population to the group under study. An example is the occurrence of second tumors in a group of patients (e.g., Wilms' tumor, ALL, etc.) where the expected number of cancers can be calculated using age-, sex-, and race-specific cancer rates for the U.S. population. When expressing risk in terms of a standardized rate, it is important to realize that the ratio may be greatly distorted if the "expected" value for the population is very small. If the population size is small and/or the incidence of the event in the general population is very low, then it is not uncommon to derive an expected value of less than one case. In this situation the standardized ratio may not be terribly meaningful.

Typically, measures of association include the point estimate as well as the calculation of the 95% confidence limits. The confidence intervals provide an important reference for the precision of the risk estimate, which is primarily a function of the size of the study population and the rate of the outcome in the reference population.

Other useful measures of risk include the calculation of cumulative risk and absolute risk. Cumulative risk is commonly used when individuals within a population are under observation for the outcome of interest for varying lengths of time. Cumulative risk or cumulative incidence represents an actuarial estimate. Therefore, as the number of individuals under observation decreases with increasing length of follow-up, the risk estimates become more unstable. Calculation of absolute risk results in determining a rate that is usually expressed as the number of events expected per fixed population measure (i.e., per 1,000 persons or per 1,000 person years). Absolute risk will typically take into consideration the risk that exists in the general population (i.e., the number of excess events).

ANALYTIC APPROACHES

The analytic approach used in the assessment of risk is highly dependent on the study design selected and type of study data collected. Generally, analytic methods can be classified as either classical or multivariate. Classical analytic methods include techniques such as contingency table analysis, parametric and nonparametric tests, and life table analyses. Confounding effects of other variables can be considered by stratification of the overall data set into multiple subgroups, resulting in one analysis unit for each level of the stratifying variable.

Multivariate methods, which include such techniques as linear regression, logistic regression, and Cox (proportional hazards) regression, use a mathematical model to adjust for covariates rather than stratification. The multivariate approach allows for the assessment of multiple variables simultaneously and an assessment of independence of each variable in predicting risk for the outcome of interest.

In a cohort study addressing a late-effects question, it is usually of interest to know not only the occurrence of the endpoint but also the interval between exposure and the outcome. Since individuals within a cohort are typically followed-up for varying lengths of time, it is essential to consider the length of observation in the analysis and thus use of life table or proportional hazards regression is essential.

ISSUES IN THE STUDY OF SECOND CANCER AND PREGNANCY OUTCOME

In the study of second malignancies and pregnancy-related outcomes, there are a number of issues to be considered. Many of these issues are applicable to most studies of late effects, but some are more relevant to those concerning second cancers and/or pregnancy outcomes.

Prior to initiation of a study it is critical to define the endpoint(s) of interest. This will allow for systematic classification of the individuals within the study. Endpoint definition should generally be established before starting the study. However, there are situations where the endpoint may be more precisely defined during or at the completion of the data collection.

Validation of study endpoints is highly desirable and sometimes essential. While the validation process can involve considerable effort, there are situations where reliance on either self-reported or "second-hand" data can cause problems. The situation with second malignancies is particularly relevant in this regard.

The potential for introduction of bias in late effects studies is an issue which should always be considered in the design, study conduct, and analysis. There are several types of bias common in studies of late effects. Examples include detection or surveillance bias where a specific group of subjects may be placed under a greater level of observation for the outcome of interest. Completeness of follow-up for individuals in a cohort is important. In the situation of assessing second cancer risk, it is possible that erroneous conclusions can be made if follow-up procedures are not systematically applied to all members of the study population. For example, if a "passive" follow-up procedure is used to assess second cancers, it is likely that as the interval from exposure increases, the number of individuals under active surveillance will decrease. Therefore, those individuals who experience an event (i.e., a second cancer) will be disproportionately represented in the follow-up intervals and result in an overestimate of the risk.

Another issue of importance is obtaining acceptably high rates of participation. If these drop very low, then the likelihood increases that the population studied is not representative of the overall target population. For studies

of late effects, it is then possible that the participants will be biased toward exposures or characteristics that may influence outcome of interest.

The study of pregnancy issues in childhood cancer survivors is one that will require careful consideration. The definition and incidence of infertility in the general population is variable and difficult to ascertain. Thus, it may not be easy to obtain an appropriate reference-base to compare childhood cancer survivors. Moreover, factors that directly impact upon issues of fertility are numerous and sometimes difficult to evaluate. Examples include religion, age, income, marital status, education, gender, race, geography, and calendar year.

SUMMARY

For future studies of late effects, it will be necessary for investigators to consider methodologic issues carefully as a means of insuring the quality of research in this increasingly important area. Recognizing the advantages and limitations in univariate and multivariate analyses will help in selecting the best analytic approach. There are many methods for denoting risk. Selection of the method will often be dependent on study design, but should also be the one believed most effective for communicating the study results.

There is little question there is a need for well-designed studies for second malignancies, especially those designed to evaluate late-occurring second cancer (i.e., in the second, third, and fourth decade following treatment). With the aging of the childhood cancer survivor population, questions regarding pregnancy issues are increasing. These questions range from those relating to fertility to others associated with mutagenesis. When considering studies of these late effects, it is important to recognize the need for selecting the most appropriate study design and statistical methods.

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